The Prospective Studies of Atherosclerosis (Proof-ATHERO) Consortium: Design and Rationale

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Short Title: Design and rationale of the Proof-ATHERO consortium

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Abstract

Atherosclerosis – the pathophysiological mechanism shared by most cardiovascular diseases – can be directly or indirectly assessed by a variety of clinical tests including measurement of carotid intima-media thickness, carotid plaque, ankle-brachial index, pulse wave velocity, and coronary artery calcium. The Prospective Studies of Atherosclerosis (Proof-ATHERO) Consortium (https://clinicalepi.i-med.ac.at/research/proof-athero/) collates de-identified individual-participant data of studies with information on atherosclerosis measures, risk factors for cardiovascular disease, and incidence of cardiovascular diseases. It currently comprises 74 studies that involve 106,846 participants from 25 countries and over 40 cities. 21 studies recruited participants from the general population (n=67,784), 16 from high-risk populations (n=22,677), and 37 as part of clinical trials (n=16,385). Baseline years of contributing studies range from April 1980 to July 2014; the latest follow-up was until June 2019. Mean age at baseline was 59 (standard deviation: 10) years and 50% were female. Over a total of 830,619 person-years of follow-up, 17,270 incident cardiovascular events (including coronary heart disease and stroke) and 13,270 deaths were recorded, corresponding to cumulative incidences of 2.1% and 1.6% per annum. The consortium is coordinated by the Clinical Epidemiology Team at the Medical University of Innsbruck, Austria. Contributing studies undergo a detailed data cleaning and harmonisation procedure before being incorporated in the Proof-ATHERO central database. Statistical analyses are being conducted according to pre-defined analysis plans and use established methods for individual-participant data meta-analysis. Capitalising on its large sample size, the multi-institutional collaborative Proof-ATHERO consortium aims to better characterise, understand, and predict the development of atherosclerosis and its clinical consequences.

Keywords: Prospective studies · Consortium · Individual-participant data · Atherosclerosis · Repeat measurements · Cardiovascular disease

Introduction

Cardiovascular diseases (CVD) are the most common cause of death and disability worldwide. According to recent estimates from the Global Burden of Disease Study, about 18 million people die of CVD in a year, which account for over 30% of all global deaths [1]. The pathophysiological mechanism shared by many CVD is atherosclerosis, a gradual and progressive hardening and narrowing of the arteries over the course of life. Initial atherosclerotic alterations can be found as early as in young adulthood [2, 3] and involve endothelial dysfunction, inflammation, and deposition of fat [4]. Advanced atherosclerotic lesions are characterised by formation of atherosclerotic plaque that can destabilise, rupture or fissure, and can ultimately lead to acute vessel occlusion or formation of a local thrombus with dislocation into distal arteries and thereby clinical sequelae [4].

Clinical and subclinical atherosclerosis can be directly or indirectly assessed using a range of different clinical tests which are simple, safe, and non-invasive, and therefore amenable for use in large-scale studies (**Fig. 1**). One of the imaging techniques for atherosclerosis most frequently used is the assessment of carotid intima-media thickness (cIMT). Using B-mode high-resolution ultrasound, the distance between the intimal and medial layer of the carotid arterial wall is quantified. Spatial resolution of this imaging technique is approximately 50 µm axially and 200 µm laterally. Ultrasound-based cIMT is considered as a marker of the early stage of atherosclerosis. It is related to unfavourable levels of traditional cardiovascular risk factors [5, 6] and has been shown to be in good accordance with "true" cIMT determined in histological studies [7]. Furthermore, increased cIMT has been associated with increased risk of cardiovascular events [8, 9].

Other scalable and commonly available measures to ascertain vessel wall pathology and dysfunction include the carotid plaque [10, 11], ankle-brachial index [12], pulse wave velocity [13], and coronary artery calcium [14–16] (**Fig. 1**). As reviewed recently [17], these measures have several strengths and weaknesses. cIMT, carotid plaque, ABI, and PWV are non-invasive and cost-effective markers, which are therefore relatively easy to implement in large clinical studies. However, disadvantages include measurement error and lack of standardisation in measurement protocols for cIMT, specificity of ABI [12], and the error associated with the measurement of travelled distance for PWV [18]. Coronary artery calcium directly quantifies presence of calcification in coronary arteries [19]. In contrast to the other mentioned markers, coronary artery calcification is assessed with computed tomography, which is more costly and exposes the study participant to radiation, thereby limiting large-scale assessments.

According to the 2019 European Society of Cardiology Guidelines for the diagnosis and management of chronic coronary syndromes, atherosclerotic plaque detection by carotid artery ultrasound, assessment of coronary artery calcium score with computed tomography, and measurement of the ankle-brachial index may be considered as risk modifiers in cardiovascular risk assessment in asymptomatic subjects [19]. Because atherosclerosis typically develops over a long period of time and only causes symptoms at an advanced stage, these measures are important tools in clinical practice to quantify atherosclerosis burden and might help inform treatment decisions.

The Prospective Studies of Atherosclerosis (Proof-ATHERO) consortium is an international consortium that brings together individual-participant data from prospective cohorts with detailed information on atherosclerosis, covariates, and incidence of CVD outcomes. The present report provides a description of broad aims of the Proof-ATHERO consortium and the principal methodology involved in collating, harmonising, and analysing study data.

Design

Objectives

Capitalising on its large sample size and the comprehensive information available, the overarching aims of the Proof-ATHERO consortium are to: (i) better characterise the natural history, communalities, and differences of different atherosclerosis measures; (ii) to provide novel insight into the determinants of atherosclerosis development and progression; and (iii) to investigate clinical consequences of atherosclerosis. In contrast to prior reports in individual studies, the large-scale data of Proof-ATHERO enables the study team to conduct power-demanding analyses, including (i) characterisation of atherosclerosis trajectories over time; (ii) determination of the shapes of associations (e.g. linear vs. curvilinear vs. threshold effects); (iii) study of potential effect modifiers (e.g. age, sex, ~~or~~ medication, or different lifestyle factors such as smoking habit); (iv) direct comparisons of the added predictive value of different atherosclerosis measures over and beyond assessment of conventional risk factors; and (v) reliable evaluation of atherosclerosis measures as surrogate markers for clinically manifest CVD endpoints. Overall, Proof-ATHERO aims to analyse world-wide available data to deliver results based on the highest scientific evidence.

Inclusion criteria

Prospective cohorts are eligible for inclusion in the Proof-ATHERO consortium if they were observational studies or clinical trials that: (i) have assessed one or more atherosclerosis measures (i.e. cIMT, carotid plaque, ankle-brachial index, pulse wave velocity, and coronary artery calcium) repeatedly (i.e. at two or more time points); (ii) have ascertained comprehensive information on CVD risk factors (e.g. lifestyle, blood-based markers, history of disease, and medication intake); and (iii) have recorded incident CVD outcomes using well-defined criteria.

A crucial foundation for the Proof-ATHERO consortium was provided by the PROG-IMT project [20]. This initiative led by Matthias Lorenz at the Goethe University at Frankfurt am Main had collated and analysed individual-participant data on the progression of cIMT and, for instance, yielded milestone publications on the association of cIMT progression with future CVD risk in the general population [8], in people with type-2 diabetes [21], and in people at high cardiovascular risk [22]. When the PROG-IMT project was completed in 2017, a majority of contributing studies (83%) decided to continue the fruitful collaboration as part of the Proof-ATHERO consortium and to jointly investigate scientific questions which go beyond the initial aims of the PROG-IMT project. The commitment by these studies gave a unique head-start to the Proof-ATHERO consortium and enabled efficient data accrual at the beginning of the initiative.

Identification and incorporation of new eligible studies is ongoing and we invite researchers to contact the coordinating centre if they wish to contribute to the Proof-ATHERO consortium.

Atherosclerosis measures

Data have been sought from investigators on carotid ultrasound parameters, ankle-brachial index, pulse wave velocity, and coronary artery calcium at baseline and any subsequent re-examinations during follow-up. Atherosclerosis measures assessed by the individual studies are summarised in **Table 1**. Parameters based on carotid ultrasound are being collected systematically on up to twelve sites (common carotid artery, carotid bifurcation, and internal carotid artery; left and right side; near and far wall) and include cIMT, vessel diameter, presence of plaques (yes *vs.* no), number of plaques, plaque thickness (height in mm), plaque area in a longitudinal view (in mm^2), and plaque morphology according to the Gray-Weale classification [23]. The methodologies which studies used to cIMT and carotid plaque are summarised in **Table S2** and **Table S3**, respectively.

Participant characteristics at the baseline and follow-up surveys

Data on participant characteristics at baseline and follow-up surveys have been sought from investigators on age, sex, ethnicity, socio-economic status, smoking, systolic and diastolic blood pressure, body-mass index, lipid markers (e.g. total cholesterol, high- and low-density lipoprotein cholesterol, triglycerides), markers of inflammation (e.g. C-reactive protein, fibrinogen, leukocyte count), markers of dysglycaemia (e.g. fasting glucose, glycated haemoglobin), use of medication (e.g. antihypertensive, antidiabetic, lipid-lowering medication), and pre-existing diseases (e.g. coronary heart disease, stroke, diabetes, or hypertension). Furthermore, in clinical trials, information on the type of interventions (and dosages, if appropriate) and on adherence to allocated regimens have been collated.

Incident disease outcomes

Data on incident disease outcomes have been collated predominantly on fatal and non-fatal CVD events, including myocardial infarction, angina pectoris, and subtypes of stroke. A detailed description of ascertainment and classification of prevalent and incident CVD is provided in **Table S4**. Studies assessed prevalent CVD at study baseline using self-report only or supplemented by objective criteria. The vast majority of the studies used objective criteria rather than self-report only for assessing incident coronary heart disease (93%) and incident stroke (90%). In addition, information on cause-specific death has been sought. In 15 studies, cause of death was ascertained based on the death certificate; 44 studies supplemented the death certificate with information from additional sources (e.g. medical records, autopsy findings). ~~Studies assessed prevalent CVD at study baseline using self-report only or supplemented by objective criteria. A detailed description of ascertainment and classification of prevalent and incident CVD is provided in **Table S4**.~~

Coordination of the consortium

The Proof-ATHERO consortium is coordinated by the Clinical Epidemiology team at the Medical University of Innsbruck, Austria. An outline of the processes involved in Proof-ATHERO coordination is provided in **Fig. 2**. Standardised data request forms are sent to eligible studies, inviting them to participate in the initiative. Upon receipt of study data, data cleaning and harmonisation are performed by a dedicated data management team using a range of tools for detecting inconsistencies and ambiguities in the data. Any queries arising during this process are clarified through direct correspondence with study investigators. Upon completion of the

data management process, study data are stored in a central database at the coordinating centre. The data management system of the coordinating centre has been implemented in *SAS 9.4*. Proposals for analyses can be submitted by all members of the Proof-ATHERO study group (i.e. all named investigators of studies contributing data to Proof-ATHERO) via the consortium's webpage. Upon receipt, proposals are reviewed by a dedicated Proof-ATHERO steering committee, which then allocates resources at the coordinating centre according to resource availability and scientific priority of the project. For contractual reasons, data are stored and analysed exclusively at the Proof-ATHERO Coordinating and Statistics Centres (Medical University of Innsbruck and University of Cambridge). At each step from development of a statistical analysis plan, to the conduct of statistical analyses, and the creation of a manuscript draft, investigators of contributing studies and expert panels are contacted for feedback and comments, therefore making use of the broad and diverse community of experts in the field involved in the initiative.

General approach to statistical analyses

For each scientific project, statistical analyses will be performed according to a pre-specified analysis plan. Statistical analyses will follow established methods in the analysis of individual-participant data [24–29]. Generally, the multi-level structure of data (e.g. multiple cohorts) will be taken into account by combining study-specific estimates using meta-analytical methods or by using mixed regression models with appropriate specification of random effects. Analyses will also involve assessments of between-studies heterogeneity. More details on specific analytical methods will be provided in publications resulting from each scientific project.

Data protection and ethics considerations

All studies contributing data to Proof-ATHERO have previously reported results and have obtained relevant local ethics approval and participants' consent. The data provided by each study remain entirely the property of the principal investigators of that study and are held in confidence by the Proof-ATHERO coordinating centre. To safeguard the identity of individuals at all stages of the analysis and to ensure compliance with data protection legislation and confidentiality guidelines, study data are transferred to the coordinating centre using encrypted connections. De-identified data are being stored securely in a central database at the coordinating centre, protected by firewalls and accessible only to authorised staff. Participants

and collaborating studies have the right to withdraw from the Proof-ATHERO consortium at any time and without giving reasons.

Characteristics of contributing studies

As of 24 January 2020, a total of 74 studies involving 106,846 participants are part of the Proof-ATHERO consortium. The designs of contributing studies and key study-level characteristics are shown in **Table 2**. In summary, 21 studies recruited participants from the general population, 16 studies were conducted in patient populations with specific pre-existing diseases (e.g. with diabetes), and 37 studies were randomised controlled trials covering a range of different patient populations. The numbers of people enrolled in these three types of studies were 67,784, 22,677, and 16,385, respectively. Baseline years ranged from April 1980 to July 2014; the last follow-up was in June 2019. Mean age at baseline was 59 years (standard deviation: 10); 50% of participants were female. **Fig. 3** demonstrates the geographical location of contributing studies. Study locations were spread across four continents and are based in 25 countries and over 40 cities. The median duration of follow-up (i.e. the time from baseline to first event or end of follow-up) was 6.1 years (interquartile range: 2.7-10.4). Over a total of 830,619 person-years of follow-up, 17,270 incident CVD events and 13,270 deaths were recorded, corresponding to cumulative incidences of 2.1% and 1.6% per annum, respectively. As Proof-ATHERO evolves further, up-to-date information on contributing studies are being made available on the consortium's webpage at https://clinicalepi.i-med.ac.at/research/proof-athero/.

Initial set of hypotheses to be tested

The large sample size and variety of data in Proof-ATHERO will enable us to test several hypotheses that are particularly power-hungry and could therefore not be addressed by previous studies. For instance, it is unclear whether cIMT progression could serve as a surrogate marker for hard cardiovascular outcomes in clinical trials [30–32]. Second, given conflicting results of prior individual studies [33–39], the comparative predictive value of cIMT measurements at different locations of the carotid artery remains to be determined in detail. Third, building on the initial insights of our recent literature-based meta-analysis [40], Proof-ATHERO will characterise in detail the association of cIMT with long-term risk of developing carotid plaque. In general, as a large-scale consortium of patient-level data, the high statistical power and

consistent approach to statistical analysis and outcome definitions of Proof-ATHERO will help to address the aforementioned and other questions with reliably than previously possible.

Strengths and limitations

Proof-ATHERO is a large consortium with a huge amount of data on atherosclerosis applying consistent approaches to data harmonisation and analysis. By inclusion of data from 25 countries and different clinical settings, the generalisability of findings will be of particular value. Our study also has several limitations. First, there were some differences between studies in how they assessed atherosclerosis measures and clinical outcomes. To address this issue, we collect meticulously a variety of study-specific characteristics, enabling us to quantify and better understand the impact of these differences in future analyses. Second, comprehensive data cleaning and harmonisation is a serious, often underestimated challenge. However, we managed to develop a sophisticated data management system that enables to transparently and effectively handle various datasets with different structures provided by the individual studies. Third, the current focus of available data lies on cIMT due to participation of multiple studies previously involved the PROG-IMT consortium [20]. Fourth, there exist several other markers for atherosclerosis, such as the assessment of endothelial function [41] with flow-mediated dilation or peripheral arterial tone, which have not been collected within Proof-ATHERO yet. Since the consortium is designed to continuously collect new data as they become available, coverage of other atherosclerosis markers will be expanded over time.

Conclusion

The Proof-ATHERO consortium is a multi-institutional collaborative project that is coordinated at the Medical University of Innsbruck. The consortium brings together large-scale data from prospective studies in the field of atherosclerosis. Proof-ATHERO combines data on CVD risk factors, repeat assessments of atherosclerosis, and clinical outcomes with cutting-edge data management and analytical tools. ~~By inclusion of data from 25 countries and different clinical settings, the generalisability of findings will be of particular value.~~ Building on these strengths, Proof-ATHERO will help to better characterise, understand, and predict the development of atherosclerosis and its clinical consequences.

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Disclosure Statement

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Author Contributions

L. Tschiderer, L. Seekircher, G. Klingenschmid, and P. Willeit are part of the coordinating centre and are responsible for data management and data analysis of the Proof-ATHERO consortium. L. Tschiderer and L. Seekircher drafted the manuscript, conducted the analyses, and interpreted the data. G. Klingenschmid interpreted the data. M. J. Sweeting provided supervision for statistical analyses. P. Willeit is responsible for the conception and design of the work, drafted the manuscript, conducted the analyses, and interpreted the data. All other authors were responsible for data acquisition. All authors revised the manuscript critically for important intellectual content approved the final version of the manuscript.

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Figure Legends

Fig. 1. Measures for quantifying atherosclerosis.

Fig. 2. Data management and analysis workflow in the Proof-ATHERO consortium.

Fig. 3. Location of studies contributing data to the Proof-ATHERO consortium as of 24 January 2020. Full study names and references are provided in **Table S1**.

Table 1. Availability of atherosclerosis measures in the Proof-ATHERO consortium as of 24 January 2020

Study acronym or first author [Reference]	cIMT	Carotid diameter	Carotid plaque	ABI	PWV	CACS
General population						
AIR	●	●	●	○	○	○
ARIC	●	●	●	●	●	○
BRUN	●	●	●	●	○	○
CAPS	●	●	●	○	○	○
CCCC	●	○	●	○	○	○
CHS	●	●	●	●	○	○
CMCS-BEIJING	●	●	●	○	○	○
DIWA	●	●	⁕	○	○	○
EAS	●	○	●	⁕	○	○
EPICARDIAN	●	●	○	○	○	○
EVA	●	●	●	○	○	○
HOORN	●	⁕	○	⁕	⁕	○
INVADE	●	○	●	●	○	○
JHS	●	○	●	●	●	●
KIHD	●	○	●	○	○	○
MESA	●	⁕	●	●	○	●
NOMAS-INVEST	●	●	●	○	○	○
PIVUS	●	●	●	⁕	○	○
PLIC	●	○	●	○	○	○
ROTTERDAM	●	●	●	⁕	⁕	⁕
SAPHIR	●	●	●	○	○	○
High-risk populations						
BK REGISTRY	●	○	●	○	○	○
CREED	●	○	○	○	○	○
CSN	●	●	●	○	○	○
Ekart	●	○	⁕	○	○	○
HD-IMT	●	●	○	○	○	○
Honda	●	○	○	○	○	○
IMPROVE	●	●	●	○	○	○
Kato	●	○	●	⁕	⁕	○
Landecho	●	○	●	○	○	⁕
NIGUARDA-MONZINO	●	●	●	○	○	○
OSACA2	●	●	○	○	○	○
Papagianni	●	○	●	○	○	○
POPROSTU	●	●	○	○	○	○
RIAS	●	○	⁕	○	○	○
SPARC	●	○	●	○	○	○
3SCO	●	●	○	○	○	○

Study acronym or first author [Reference]	cIMT	Carotid diameter	Carotid plaque	ABI	PWV	CACS
Clinical trials						
ACAPS	●	○	○	○	○	○
ALLO-IMT	●	○	○	○	●	○
ASAP-NL	●	●	⁕	○	○	○
ATIC	●	○	○	○	○	○
AUDITOR	●	○	○	○	○	○
BAS	●	○	○	○	●	○
BK REGISTRY II	●	○	●	○	○	○
CAMERA	●	○	●	○	○	○
CAPTIVATE	●	●	○	○	○	○
CERDIA	●	○	○	○	○	○
CONTRAST	●	○	●	○	○	○
EGE STUDY	●	○	●	○	⁕	⁕
ENHANCE	●	○	●	○	○	○
FACIT	●	●	○	○	○	○
GRACE	●	○	⁕	⁕	○	○
Gresele	●	○	○	⁕	○	○
HART	●	○	⁕	⁕	○	○
KIMVASC	●	○	○	○	⁕	○
LIFE-ICARUS	●	●	●	○	○	○
Masia	●	○	●	●	○	○
MAVET	●	○	○	○	○	○
MEDICLAS	●	●	○	○	⁕	○
MG600	●	●	●	○	●	○
Nakamura II	●	●	⁕	○	⁕	○
OPAL	●	⁕	○	○	○	○
PERIOCARDIO	●	●	○	○	⁕	○
PREVEND IT	●	○	○	○	○	○
RADIANCE I	●	●	○	○	○	○
RADIANCE II	●	●	○	○	○	○
REGRESS	●	○	○	○	○	○
RIS	●	●	⁕	○	○	○
Safarova	●	○	⁕	⁕	⁕	○
SECURE	●	○	⁕	⁕	○	○
STARR	●	○	⁕	⁕	○	○
STOP-NIDDM	●	○	○	○	○	○
VITAL	●	○	○	○	○	○
WELCOME	●	○	●	○	○	○

● =available and provided, ⁕ =available but not provided, ○ =not available. ABI, ankle-brachial index; CACS, coronary artery calcium score; cIMT, carotid intima-media thickness; PWV, pulse wave velocity. Full study names and references are provided in **Table S1**.

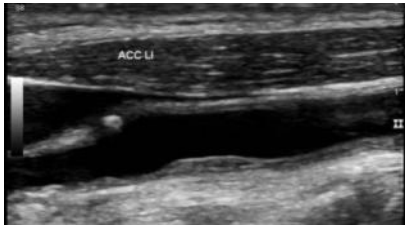
Table 2. Design and descriptive summary of studies in the Proof-ATHERO consortium

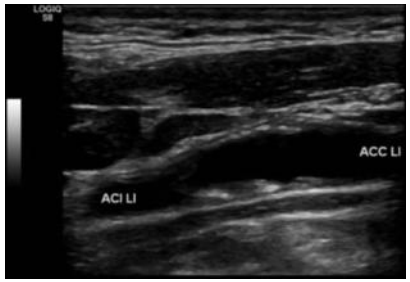
Study acronym or first author	Country	Population source	Population type	Years of baseline	No.	♀, %	Mean age, years (SD)
General population							
AIR	Sweden	Population register	General population	1995-97	391	0	58 (0.1)
ARIC	USA	Household listings	General population	1986-90	15,121	55	54 (6)
BRUN	Italy	Population register	General population	1990	933	49	59 (11)
CAPS	Germany	Electoral rolls	General population	1995-00	6,970	51	51 (13)
CCCC	Taiwan	Community screening	General population	1990-91	3,602	53	55 (12)
CHS	USA	Medicare lists	General population	1989-93	5,888	57	73 (6)
CMCS-BEIJING	China	Population register	General population	2002	1,324	53	60 (8)
DIWA	Sweden	Population register	General population	2001-04	644	100	64 (0.3)
EAS	Scotland	GP lists	General population	1987-88	1,115	50	64 (6)
EPICARDIAN	Spain	Population register	General population	1993-04	446	59	68 (12)
EVA	France	Electoral rolls	General population	1992-93	1,135	59	65 (3)
HOORN	Netherlands	Population register	General population	1999-01	780	50	69 (7)
INVADE	Germany	Insurance company	General population	2001-03	3,908	59	68 (8)
JHS	USA	Household listings	General population	2000-04	3,883	63	55 (13)
KIHD	Finland	Population register	General population	1987-89	1,399	0	52 (6)
MESA	USA	Household listings	General population	2000-02	6,814	53	62 (10)
NOMAS-INVEST	USA	Random digit dialing	General population	1993-01	856	62	66 (8)
PIVUS	Sweden	Population register	General population	2001-04	1,016	50	70 (0.0)
PLIC	Italy	Hospital	General population	1998-03	1,782	59	55 (11)
ROTTERDAM	Netherlands	Population register	General population	1990-93	7,983	61	71 (10)
SAPHIR	Austria	GP lists/advert	General population	1999-02	1,794	37	52 (6)
High-risk populations							
BK REGISTRY	Korea	Hospital	CHD	2000-07	1,000	44	60 (10)
CREED	Italy	Hospital	On haemodialysis/CAPD	1997-98	138	41	60 (16)
CSN	Italy	GP lists	Hypertension	1980-14	14,158	44	53 (13)
Ekart	Slovenia	Hospital	On haemodialysis	1996-05	54	50	55 (15)
HD-IMT	Serbia	Hospital	On haemodialysis	2004-05	85	39	59 (12)
Honda	Japan	Hospital	On haemodialysis	2005-07	313	39	61 (13)
IMPROVE	Multinational	Hospital/community screening	≥3 CVD RFs	2004-05	3,703	52	64 (5)
Kato	Japan	Hospital	On haemodialysis	2008-09	284	30	64 (12)
Landecho	Spain	Hospital	Early kidney disease	1999-11	250	12	55 (10)
NIGUARDA-MONZINO	Italy	Hospital	Lipid clinic patients/ CVD RFs	1984-10	1,564	41	56 (12)
OSACA2	Japan	Hospital	≥1 atherosclerotic RF	2000-03	291	40	65 (9)
Papagianni	Greece	Hospital	On haemodialysis	2001	83	46	58 (15)
POPROSTU	Poland	Hospital	T1DM	1999	96	33	24 (6)
RIAS	Switzerland	Hospital	≥1 CVD RF/CVD	1999-00	145	43	64 (13)
SPARC	Canada	Hospital	Carotid plaque	2006-08	349	43	71 (9)
3SCO	Japan	Hospital	≥1 CVD RF	2007	164	74	80 (6)
Clinical trials							
ACAPS	USA	Mailing lists/ community screening	LDL-C 130-189 mg/dL	1989-90	919	48	62 (8)
ALLO-IMT	Scotland	Hospital	Ischaemic stroke/TIA	2009-10	80	43	68 (10)
ASAP-NL	Netherlands	Hospital	Heterozygous FH	1997-98	325	61	49 (11)
ATIC	Netherlands	Hospital	Chronic renal failure	2001-02	93	43	53 (12)
AUDITOR	Multinational	Hospital	Obesity+metabolic syndrome	2005-06	661	49	63 (6)
BAS	China	Community screening	cIMT↑	2010	125	63	57 (5)
BK REGISTRY II	Korea	Hospital	Coronary stent	2000-03	205	32	60 (10)
CAMERA	Scotland	Hospital/GP lists	CHD	2009-11	173	23	63 (8)
CAPTIVATE	Multinational	Hospital	Heterozygous FH	2004-05	719	NP	NP
CERDIA	Netherlands	Hospital	T2DM	1999-01	250	53	58 (11)
CONTRAST	Multinational	Hospital	On haemodialysis	2004-09	714	38	64 (14)

EGE STUDY	Turkey	Hospital	On haemodialysis	2005-06	644	46	59 (14)
ENHANCE	Multinational	Hospital	Heterozygous FH	2002-06	720	49	47 (9)
FACIT	Netherlands	Municipal/blood bank registries	General population	2000-01	819	28	60 (6)
GRACE	Multinational	Hospital	Dysglycaemia+CVD RFs/CVD	2003-05	1,189	36	63 (8)
Gresele	Multinational	Hospital	Peripheral arterial disease	2003-05	442	21	67 (9)
HART	Canada	Hospital/GP lists	CVD/DM+≥1 CVD RF	1999-00	925	24	69 (7)
KIMVASC	Scotland	GP lists	CVD/hypertension/DM	2011-12	80	45	77 (5)
LIFE-ICARUS	Multinational	Hospital	Hypertension+LVH	1996-97	83	27	67 (6)
Masia	Spain	Hospital	HIV+≥2 CVD RFs	2006-07	68	10	52 (11)
MAVET	Australia	Newspaper advert	Smokers	1994-95	408	54	64 (6)
MEDICLAS	Multinational	Hospital	HIV	2003-05	48	0	42 (10)
MG600	Brazil	Hospital	Hypertension	2010-11	35	100	55 (7)
Nakamura II	Japan	Hospital	Chronic renal failure	2001	50	40	53 (7)
OPAL	Multinational	Hospital/GP lists/other[a]	General population	1997-99	866	100	59 (7)
PERIOCARDIO	Australia	Health facilities	Aboriginal Australians	2010-12	273	42	41 (10)
PREVEND IT	Netherlands	Population register	Microalbuminuria	1998-99	864	35	51 (12)
RADIANCE I	Multinational	Hospital	Heterozygous FH	2003-04	904	51	46 (13)
RADIANCE II	Multinational	Hospital	Mixed dyslipidaemia	2003-06	752	36	57 (8)
REGRESS	Netherlands	Hospital	CHD+TC 155-310 mg/dL	1989-91	255	0	56 (8)
RIS	Sweden	Hospital	Hypertension+≥1 CVD RF	1987-89	164	0	66 (5)
Safarova	Russia	Hospital	CHD	2007-09	60	0	55 (6)
SECURE	Canada	Hospital	CVD/DM+≥1 CVD RF	1994-95	731	24	66 (7)
STARR	Multinational	Hospital/GP lists/other[b]	Dysglycaemia	2001-03	1,320	55	53 (11)
STOP-NIDDM	Germany	High-risk population screening	Dysglycaemia	1996-98	119	42	54 (7)
VITAL	Netherlands	Hospital	Indication for statin use	2002-04	199	41	49 (12)
WELCOME	UK	Hospital	NAFLD	2010-11	103	42	51 (11)
Total				**1980-14**	**106,846**	**50**	**59 (10)**

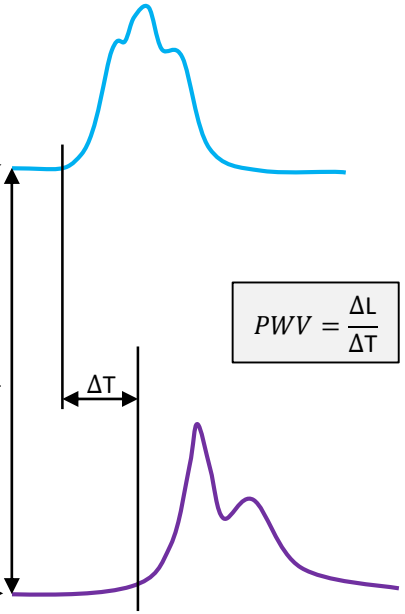
CAPD, continuous ambulatory peritoneal dialysis; CHD, coronary heart disease; cIMT, carotid intima-media thickness; CVD, cardiovascular disease; DM, diabetes mellitus; FH, familial hypercholesterolaemia; GP, general practitioner; HIV, human immunodeficiency virus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LDL-C, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; NAFLD, non-alcoholic fatty liver disease; NP, not provided; RF, risk factor; SD, standard deviation; TC, total cholesterol; TIA, transient ischaemic attack; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus. Full study names and references are provided in **Table S1**. [a]Existing ongoing population-based cohorts and advertisements in local print and broadcast media. [b]Public advertising and news reports in the media, internet items, referral from relatives, poster displays, diabetes screening fairs and direct mailing campaigns.

Carotid ultrasound

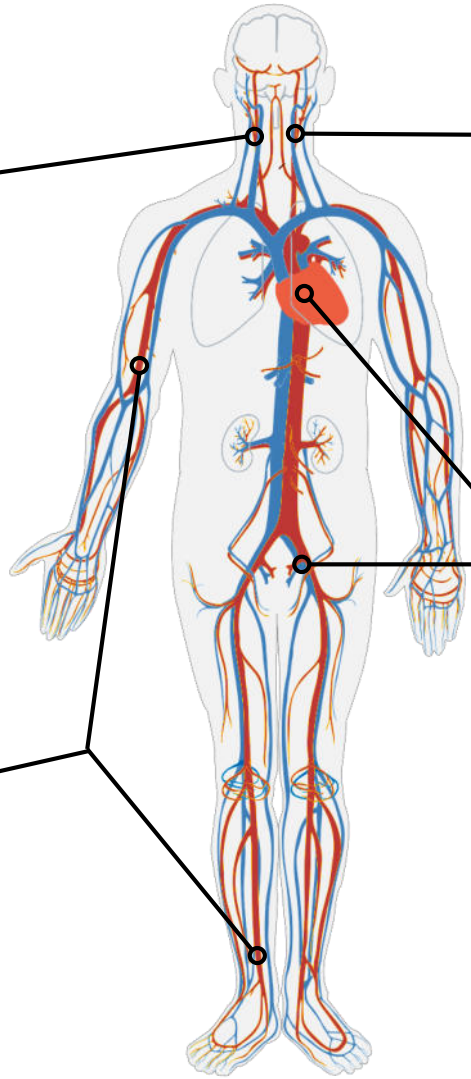




Pulse wave velocity

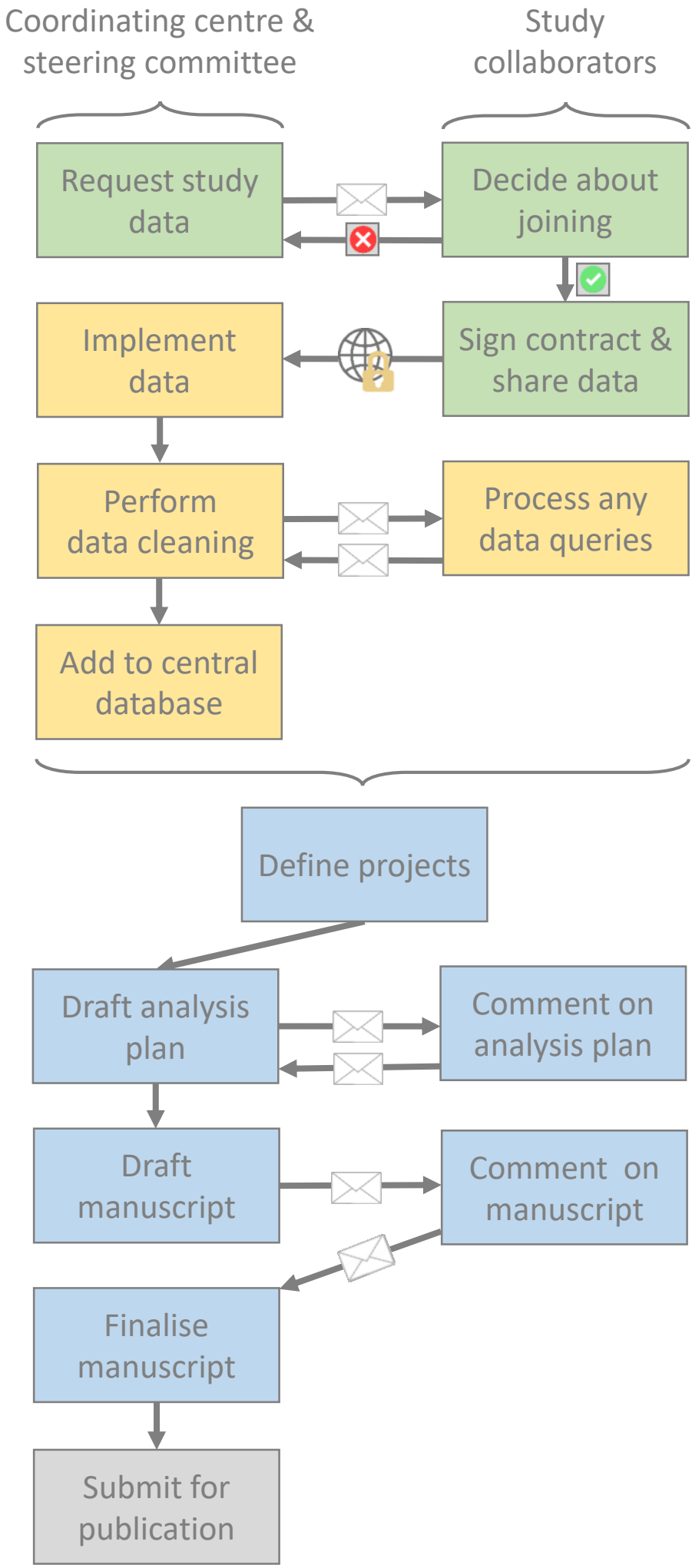


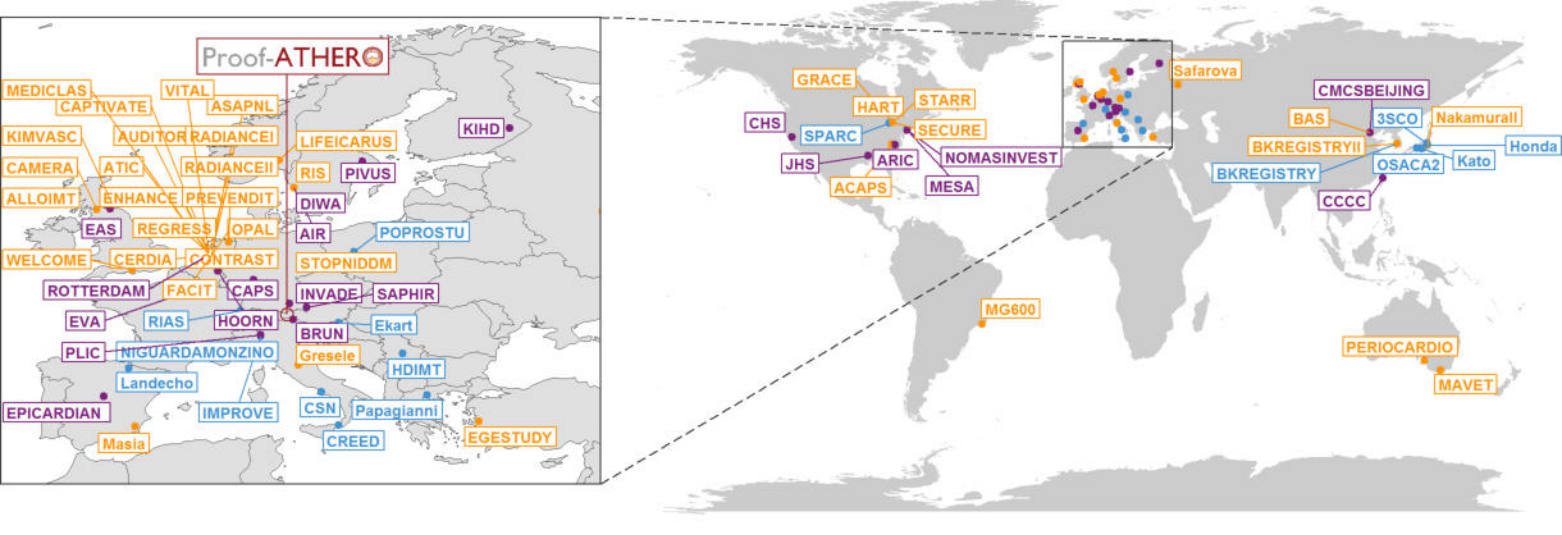
$$PWV = \frac{\Delta L}{\Delta T}$$



Ankle-brachial index

Coronary artery calcium


Coordinating centre & steering committee
Study collaborators
Request study data
Decide about joining
Implement data
Sign contract & share data
Perform data cleaning
Process any data queries
Add to central database
Define projects
Draft analysis plan
Comment on analysis plan
Draft manuscript
Comment on manuscript
Finalise manuscript
Submit for publication


Proof-ATHERO
MEDICLAS
CAPTIVATE
VITAL
ASAPNL
KIMVASC
AUDITOR
RADIANCEI
LIFEICARUS
KIHD
CAMERA
ATIC
RADIANCEII
RIS
PIVUS
ALLOIMT
ENHANCE
PREVENDIT
DIWA
EAS
REGRESS
OPAL
AIR
POPROSTU
WELCOME
CERDIA
CONTRAST
STOPNIDDM
ROTTERDAM
FACIT
CAPS
INVADE
SAPHIR
EVA
RIAS
HOORN
Ekart
BRUN
PLIC
NIGUARDAMONZINO
Gresele
HDIMT
Landecho
EPICARDIAN
IMPROVE
CSN
Papagianni
Masia
CREED
EGESTUDY
GRACE
HART
STARR
CHS
SPARC
SECURE
JHS
ARIC
NOMASINVEST
ACAPS
MESA
Safarova
CMCSBEIJING
BAS
3SCO
Nakamurall
BKREGISTRYII
Honda
OSACA2
Kato
BKREGISTRY
CCCC
MG600
PERIOCARDIO
MAVET
General population
High-risk population
Clinical trial

The Prospective Studies of Atherosclerosis (Proof-ATHERO) consortium: Design and rationale

Tschiderer, Seekircher *et al.*

Electronic Supplementary Material

Table S1. Study acronyms, full study names, and study references in the Proof-ATHERO consortium

Study acronym or first author	Ref.	Full study name
General population		
AIR	[1]	Atherosclerosis and Insulin Resistance Study
ARIC	[2]	Atherosclerosis Risk in Communities Study
BRUN	[3]	Bruneck Study
CAPS	[4]	Carotid Atherosclerosis Progression Study
CCCC	[5]	Chin-Shan Community Cardiovascular Cohort
CHS	[6]	Cardiovascular Health Study
CMCS-BEIJING	[7]	Chinese Multi-Provincial Cohort Study (Beijing)
DIWA	[8]	Diabetes and Insulin Resistance in Women Study
EAS	[9]	Edinburgh Artery Study
EPICARDIAN	[10]	Epidemiología Cardiovascular en los Ancianos en España Study
EVA	[11]	Étude sur la Vieillissement Artériel Study
HOORN	[12]	Hoorn Study
INVADE	[13]	Interventionsprojekt zerebrovaskuläre Erkrankungen und Demenz im Landkreis Ebersberg
JHS	[14]	Jackson Heart Study
KIHD	[15]	Kuopio Ischemic Heart Disease Risk Factor Study
MESA	[16]	Multi-Ethnic Study of Atherosclerosis
NOMAS-INVEST	[17]	Northern Manhattan Study and The Oral Infections and Vascular Disease Epidemiology Study
PIVUS	[18]	Prospective Investigation of the Vasculature in Uppsala Seniors Study
PLIC	[19]	Presence and Progression of Lesions in Carotid Arteries Study
ROTTERDAM	[20]	Rotterdam Study
SAPHIR	[21]	Salzburg Atherosclerosis Prevention Program in Subjects at High Individual Risk
High-risk populations		
BK REGISTRY	[22]	BK Registry Study
CREED	[23]	Cardiovascular Risk Extended Evaluation in Dialysis Patients
CSN	[24]	Campania Salute Network
Ekart	[25]	Study Ekart et al.
HD-IMT	[26]	HD-IMT Study
Honda	[27]	Study Honda et al.
IMPROVE	[28]	Carotid Intima Media Thickness and IMT-Progression as Predictors of Vascular Events in a High Risk European Population Study
Kato	[29]	Study Kato et al.
Landecho	[30]	Study Landecho et al.
NIGUARDA-MONZINO	[31]	Niguarda-Monzino Study
OSACA2	[32]	Osaka Follow-up Study for Carotid Atherosclerosis 2
Papagianni	[33]	Study Papagianni et al.
POPROSTU	[34]	Poznań Prospective Study of Type-1 Diabetic Patients
RIAS	[35]	Resistive Index in Atherosclerosis Study
SPARC	[36]	SPARC Study
3SCO	[37]	Hiroshima-Shobara-Soryo Cohort
Clinical trials		
ACAPS	[38]	Asymptomatic Carotid Artery Progression Study
ALLO-IMT	[39]	ALLO-IMT Study
ASAP-NL	[40]	Atorvastatin vs. Simvastatin on Atherosclerosis Progression Study
ATIC	[41]	Anti-oxidant Therapy in Chronic Renal Insufficiency Study
AUDITOR	[42]	Atherosclerosis Underlying Development Assessed by Intima-Media Thickness in atients on Rimonabant Study
BAS	[43]	Beijing Atherosclerosis Study
BK REGISTRY II	[44]	BK Registry II Study
CAMERA	[45]	Carotid Atherosclerosis - Metformin for Insulin Resistance Study
CAPTIVATE	[46]	Carotid Atherosclerosis Progression Trial Investigating Vascular ACAT Inhibition
CERDIA	[47]	Cerivastatin in Diabetes Trial
CONTRAST	[48]	Convective Transport Study
EGE STUDY	[49]	Ege Study

ENHANCE	[50]	Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis egression Trial
FACIT	[51]	Folic Acid and Carotid Intima-media Thickness Study
GRACE	[52]	Glucose Reduction and Atherosclerosis Continuing Evaluation Study
Gresele	[53]	Study Gresele at al.
HART	[54]	Homocysteine and Atherosclerosis Reduction Trial
KIMVASC	[55]	KIMVASC Study
LIFE-ICARUS	[56]	Losartan Intervention For Endpoint Reduction in Hypertension - Insulin Carotids US Scandinavia Study
Masia	[57]	Study Masiá et al.
MAVET	[58]	Melbourne Atherosclerosis Vitamin E Trial
MEDICLAS	[59]	Metabolic Effects of Different Classes of Antiretrovirals Study
MG600	[60]	Effects of Magnesium Supplementation on Vascular Structure and Function in Hypertensive Patients Study
Nakamura II	[61]	Study Nakamura et al. II
OPAL	[62]	Osteoporosis Prevention and Arterial Effects of Tibolone Study
PERIOCARDIO	[63]	PerioCardio Study
PREVEND IT	[64]	Prevention of Renal and Vascular Endstage Disease Intervention Trial
RADIANCE I	[65]	Rating Atherosclerosis Disease Change by Imaging with a New CETP Inhibitor 1 Trial
RADIANCE II	[66]	Rating Atherosclerosis Disease Change by Imaging with a New CETP Inhibitor 2 Trial
REGRESS	[67]	Regression Growth Evaluation Statin Study
RIS	[68]	Risk Factor Intervention Study
Safarova	[69]	Study Safarova at al.
SECURE	[70]	Study to Evaluate Carotid Ultrasound Changes in Patients Treated with Ramipril and Vitamin E
STARR	[71]	Study of Atherosclerosis with Ramipril and Rosiglitazone
STOP-NIDDM	[72]	Study to Prevent Non-Insulin-Dependent Diabetes Mellitus
VITAL	[73]	Vital Study
WELCOME	[74]	Wessex Evaluation of Fatty Liver and Cardiovascular Markers in NAFLD with Omacor Therapy Trial

Table S2. Ascertainment of cIMT in the Proof-ATHERO consortium

Study acronym or first author	cIMT definition											Measurement features							
	Section			Side			Wall			Type									
	CCA	BIF	ICA	Right	Left	Average	Near	Far	Average	Mean	Max	Plaque avoided	Multiple scans	ECG gated	Same machine type	Same sonographer	Central reading	Angle control	Edge detection
General population																			
AIR	●	●	○	●	●	●	○	●	●	●	●	–	–	+	+	+	+	–	+[e]
ARIC	●	●	●	●	●	●	●	●	●	●	●	–	+	+	+	–	+	+	–
BRUN	●	●	●	●	●	●	○	●	●	●	●	+	–	+	–	+	–	+	–
CAPS	●	●	●	●	●	●	○	●	●	●	○	–	–	+	+	–	+	–	+[d]
CCCC	●	○	●	●	●	●	○	●	●	○	●	+	+	+	+	–	–	+	–
CHS	●	○	●	●	●	●	●	●	●	○	●	–	+[a]	–	+	–	+	+	–
CMCS-BEIJING	●	●	●	●	●	●	○	○	●	●	●	+	–	–	–	–	+	+	–/+[e]
DIWA	●	●	○	●	●	●	○	●	●	●	●	–	–	+	+	+	+	–	+[e]
EAS	●	○	○	●	●	●	○	●	●	●	●	–	–	–	+	–	+	–	–
EPICARDIAN	●	●	●	●	●	●	○	●	●	●	○	+	+	–	+	+	–	+	–
EVA	●	○	○	●	●	●	○	●	●	●	○	+	–	–	+	–	+	+	+[d]
HOORN	●	○	○	●	○	●	○	●	●	●	○	+	+	+	+	+	+	+	+[d]
INVADE	●	○	○	●	●	●	○	●	●	●	○	+	+	–	+	+	+	+	+[d]
JHS	●	●	●	●	●	●	●	●	●	●	●	–	+	+	+	–	+	+	–
KIHD	●	○	○	●	●	●	○	●	●	●	●	–	–	–	–	–	+	+	+[e]
MESA	●	○	●	●	●	●	○	○	●	●	●	+	+[ab]	+	+	NR	+	+	+[d]
NOMAS-INVEST	●	●	●	●	●	●	●	●	●	●	●	+	+[b]	–	+	+	+	+	+[e]
PIVUS	●	○	○	●	●	●	○	●	●	●	●	NR	–	+	+	+	+	–	+[e]
PLIC	●	○	○	●	●	●	○	●	●	●	●	+	+[b]	+	+	+	+	–	+
ROTTERDAM	●	○	○	●	●	●	●	●	●	●	●	–	+	+	+	–	+	–	–
SAPHIR	●	●	●	●	●	●	○	○	●	●	○	+	+	–	+	+	+	+	–
High-risk populations																			
BK REGISTRY	●	●	○	●	●	●	○	●	●	●	○	+	+	+	+	+	+	+	+[e]
CREED	●	○	○	○	○	●	○	●	●	●	○	+	–	+	+	+	–	+	–
CSN	●	●	●	●	●	●	●	●	●	○	●	–	–	–	+	–	+	–	–
Ekart	●	●	●	●	●	●	○	●	●	●	○	+	+	–	+	+	+	+	–
HD-IMT	●	○	○	●	○	●	○	●	●	○	●	–	–	+	+	+	–	–	–
Honda	●	○	○	●	●	●	○	●	●	●	●	–	–	–	–	–	–	–	–
IMPROVE	●	●	●	●	●	●	○	●	●	●	●	–	+	+[b]	+	–	+	+	+[e]
Kato	●	○	○	○	○	●	○	●	●	●	●	+	–	–	+	+	+	+	+[e]
Landecho	●	○	○	●	●	●	○	○	●	○	●	+	–	–	–	–	–	–	–
NIGUARDA-MONZINO	●	●	●	●	●	●	●	●	●	○	●	–	–	–	–	–	–	+	–
OSACA2	●	●	●	●	●	●	●	●	●	●	●	–	+[b]	–	+	–	+	–	–
Papagianni	○	●	○	●	●	●	○	●	●	●	●	+	–	+	+	+	+	–	–
POPROSTU	●	○	○	●	○	●	○	●	●	●	●	+	+	–	+	+	+	+	+[d]
RIAS	●	○	○	●	●	●	○	●	●	●	○	+	+	+	+	–	–	–	–
SPARC	●	○	○	●	●	●	○	●	●	●	○	+	+	–	NR	NR	+	–	–
3SCO	●	●	●	●	●	●	●	●	●	●	●	–	–	–	+	–	–	–	–
Clinical trials																			
ACAPS	●	●	●	●	●	●	○	○	●	○	●	–	–	+	+	–	+	+	+[e]
ALLO-IMT	●	●	●	●	●	●	●	●	●	●	●	–	–	+	+	+	+	+	+[de]
ASAP-NL	●	●	●	●	●	●	●	●	●	●	○	–	–	–	+	–	+	+	+[e]
ATIC	●	○	○	●	○	●	○	●	●	●	○	+	+	+	+	+	+	–	+[d]
AUDITOR	●	●	●	●	●	●	○	●	●	●	○	–	–	+	+	–	+	+	–
BAS	●	○	○	○	○	●	●	○	●	●	○	+	–	–	+	–	+	–	–
BK REGISTRY II	●	●	●	○	●	●	○	●	●	●	○	+	+	+	+	+	+	+	+[e]
CAMERA	●	○	○	●	●	●	○	●	●	●	○	+	–	+	+	+	+	+	+[e]
CAPTIVATE	●	●	●	●	●	●	●	●	●	●	●	–	+	–	+	–	+	+	+[e]
CERDIA	●	●	●	●	○	●	○	○	●	●	●	+	–	+	+	–	+	+	+[e]
CONTRAST	●	○	○	●	●	●	●	●	●	●	●	–	+	+	–	–	+	+	–

EGE STUDY	●	○	○	●	●	●	○	●	●	●	○	+	NR	NR	+	+	NR	NR	NR
ENHANCE	●	●	●	●	●	●	○	●	●	●	●	–	+[c]	–	+	–	+	+	+[e]
FACIT	●	○	○	○	○	●	○	○	●	●	●	–	+	+	+	–	+	+	+[d]
GRACE	●	●	●	●	●	●	●	●	●	●	●	–	+	–	–	–	+	+	–
Gresele	●	○	○	●	○	●	●	○	●	●	●	+	–	–	+	+	+	+	+[d]
HART	●	●	●	●	●	●	●	●	●	●	●	–	+	–	–	–	+	+	–
KIMVASC	●	○	○	●	●	●	○	●	●	●	○	+	–	–	+	+	+	–	–
LIFE-ICARUS	●	○	○	●	●	●	○	●	●	●	○	+	+[b]	+	+	+	+	+	+[e]
Masia	●	○	○	●	●	●	○	●	●	●	●	NR	NR	NR	NR	NR	NR	NR	NR
MAVET	●	○	○	○	○	●	○	○	●	○	●	NR	+	+	+	+	+	+	–
MEDICLAS	●	○	○	●	○	●	○	○	●	●	○	+	+	–	+	+	+	–	–
MG600	●	○	○	●	●	●	○	○	●	●	●	+	+	+	+	+	–	–	–
Nakamura II	●	●	●	●	●	●	○	●	●	●	●	+	–	+	+	+	+	+	–
OPAL	●	●	●	●	●	●	●	●	●	●	●	–	+	+	+	–	+	+	–
PERIOCARDIO	●	○	○	●	●	●	○	●	●	●	●	–	+	+	+	–	+	+	+[e]
PREVEND IT	●	○	○	○	●	●	○	●	●	●	○	+	+	+	+	–	+	+	+[d]
RADIANCE I	●	●	●	●	●	●	●	●	●	●	●	–	+[c]	+	+	–	+	+	+[e]
RADIANCE II	●	●	●	●	●	●	●	●	●	●	●	–	+[c]	+	+	–	+	+	+[e]
REGRESS	●	●	●	●	●	●	●	●	●	●	●	–	–	–	–	–	+	+	+[d]
RIS	●	●	○	●	○	●	○	●	●	●	●	+	+	+	+	+	+	+	+[d]
Safarova	●	○	○	●	●	●	○	●	●	●	○	+	–	+	+	+	+	+	+[e]
SECURE	●	●	●	●	●	●	●	●	●	○	●	–	+	–	–	–	+	+	–
STARR	●	●	●	●	●	●	●	●	●	●	●	–	+	–	–	–	+	+	–
STOP-NIDDM	●	○	○	●	●	●	○	●	●	●	●	NR	+	+	+	–	NR	NR	NR
VITAL	●	○	○	●	○	●	○	●	●	●	○	NR	NR	NR	NR	NR	NR	NR	NR
WELCOME	●	○	○	●	●	●	○	●	●	●	○	+	+	+	+	+	+	+	+[d]

●=provided, ○=not provided; BIF=carotid bifurcation, CCA=common carotid artery, cIMT=carotid intima-media thickness, ECG=electrocardiography, ICA=internal carotid artery, IMT=intima-media thickness. Full study names and references are provided in **Table S1**. [a]ICA only. [b]Only in a subset of the study population. [c]Only at baseline and final follow-up. [d]Automated. [e]Semi-automated.

Table S3. Ascertainment of carotid plaque in the Proof-ATHERO consortium

Study acronym or first author	Parameters					Detailed information on carotid plaque definition
	Status	Amount	Thickness	Area	Density[a]	
General population						
AIR	●	●	●	●	●	Distinct area with an IMT >50% thicker than that of neighbouring sites
ARIC	●	●	○	○	○	If two of three conditions are met: (1) wall shape (protrusion into the lumen, loss of alignment, rough boundary), (2) wall texture (brighter echoes than adjacent boundaries), and (3) wall thickness (IMT ≥1.5 mm)
BRUN	●	●	●	○	○	Based on (1) wall surface (protrusion into the lumen or roughness of the arterial boundary) and (2) wall texture (echogenicity)
CAPS	●	○	○	○	○	Focal protrusion of ≥1.8 mm
CCCC	●	●	○	○	○	Grading as (1) normal or no observable plaque, (2) one small plaque with diameter stenosis <30%, (3) one medium plaque with 30-49% diameter stenosis or multiple small plaques, (4) one large plaque with 50-99% diameter stenosis or multiple plaques with at least one medium plaque, and (5) 100% occlusion
CHS	●	○	○	○	●	Definition based on the greatest wall protrusion (i.e. IMT) and grading based on lesion surface, echogenicity, and texture characteristics as (1) no plaque (i.e. smooth surface and normal density and morphology), (2) high-risk plaque (i.e. irregular/ulcerated surface, echolucent, or heterogeneous texture), and (3) intermediate-risk plaque (i.e. any other combinations of lesion characteristics)
CMCS-BEIJING	●	○	●	●	○	IMT ≥1.3 mm or focal structure encroaching into arterial lumen of ≥0.5 mm or ≥50% of surrounding IMT
EAS	●	○	●	○	○	IMT >1.2 mm with advanced atherosclerotic plaque defined as IMT >2 mm
EVA	●	●	●	○	○	Localised echo structures encroaching into the vessel lumen with a distance ≥1 mm between media-adventitia interface and lesion surface facing the lumen
INVADE	●	○	○	○	○	Focal structure encroaching into the arterial lumen ≥0.5 mm or ≥50% of the surrounding IMT, or IMT >1.5 mm as measured from the media-adventitia interface to the intima-lumen interface
JHS	●	○	○	○	○	If two of three conditions are met: (1) wall shape (protrusion into the lumen, loss of alignment, rough boundary), (2) wall texture (brighter echoes than adjacent boundaries), and (3) wall thickness (IMT ≥1.5 mm)
KIHD	●	○	○	○	○	Distinct area either with mineralisation (bright echo, often producing a typical echogenic shadow) or with focal protrusion into the lumen
MESA	●	○	○	○	●	Discrete, focal thickening ≥1.5 mm or ≥50% greater than the surrounding IMT
NOMAS-INVEST	●	●	●	●	○	Focal wall thickening or protrusion into the lumen >50% greater than the surrounding thickness
PIVUS	●	○	●	●	○	Local thickening of the intima-media by >50% vs. surrounding IMT
PLIC	●	○	○	○	○	Focal plaque >1.3 mm in longitudinal resolution, lateral, or medial angle
ROTTERDAM	●	○	○	○	○	Focal widening relative to adjacent segments, with protrusion into the lumen with calcified deposits or both calcified and non-calcified material
SAPHIR	●	○	○	○	○	Grading as (1) normal, (2) vessel wall thickening <1 mm, (3) one minimal plaque ≤2 mm, (4) two moderate plaques ≤3 mm, (5) severe plaque >3 mm, and (6) completely obstructed lumen
High-risk populations						
BK REGISTRY	●	○	●	○	○	Focal structure encroaching into arterial lumen by ≥50% of surrounding IMT or thickness >1.2 mm
CSN	●	○	○	○	○	IMT >1.5 mm
IMPROVE	●	●	●	●	○	IMT ≥1.5 mm
Kato	●	○	○	○	○	IMT >1 mm
Landecho	●	○	○	○	○	Echogenic structures encroaching on the vessel's lumen with a distinct area 50% greater than the IMT of neighbouring sites
NIGUARDA-MONZINO	●	●	●	○	○	IMT ≥1.5 mm
Papagianni	●	○	○	○	○	Faint grey echoes or bright white echoes protruding into the arterial lumen
SPARC	●	○	○	●	○	Focal thickening >1 mm
Clinical trials						
BK REGISTRY II	●	○	●	○	○	Localised thickening >1.2 mm not involving the whole carotid artery
CAMERA	●	●	○	○	○	IMT ≥1.5 mm or focal encroachment into the arterial lumen ≥0.5 mm

CONTRAST	●	●	○	○	○	Grading as (1) no plaque, (2) minimal plaque, (3) moderate plaque, and (4) severe plaque, where a moderate or severe plaque was generally defined as a focal structure that encroaches into the arterial lumen or demonstrates a thickness >1.5 mm
EGE STUDY	●	○	●	○	○	NR
ENHANCE	●	○	○	○	○	IMT >1.3 mm
LIFE-ICARUS	●	○	○	○	○	Semi-quantitative grading of the amount of atherosclerotic lesions as (1) none, (2) very few, (3) few, (4) some, and (5) several
Masia	●	○	○	○	○	NR
MG600	●	○	○	○	○	IMT ≥1.5 mm
WELCOME	●	○	○	○	○	Focal thickening ≥50% greater than the surrounding wall or focal region with IMT >1.5 mm protruding into the lumen distinct from adjacent boundary

●=provided, ○=not provided; IMT, intima-media thickness; NR, not reported. Full study names and references are provided in **Table S1**. [a]Density according to the Gray-Weale classification.

Table S4. Assessment of prevalent and incident disease in the Proof-ATHERO consortium

Study acronym or first author	Prevalent disease			Incident events		
	CHD	Stroke	Diabetes	CHD	Stroke	Death
General population						
AIR	+	+	++	++	++	*
ARIC	++	++	++	++	++	**
BRUN	++	++	++	++	++	**
CAPS	+	+	+	++	++	**
CCCC	++	++	++	NR	++	*
CHS	++	++	++	++	++	**
CMCS-BEIJING	++	++	++	++	++	**[c]
DIWA	+	+	++	++	++	*
EAS	++	+	+	++	++	**[c]
EPICARDIAN	++	++	++	++	++	*
EVA	+	+	++	++[b]	++[b]	**
HOORN	+/++	+/++	++	++	++	**
INVADE	++	++	++	++	++	**
JHS	+	+	++	+	+	–[a]
KIHD	++	+	++	++	++	**
MESA	+	–[a]	++	++	++	**
NOMAS-INVEST	+	+	++	++	++	**
PIVUS	+	+	+/++	++	++	**
PLIC	NR	NR	++	NR	NR	NR
ROTTERDAM	++	++	++	++	++	**
SAPHIR	++	++	++	++	++	**
High–risk populations						
BK REGISTRY	++	–	++	++	++	*/**
CREED	NR	NR	NR	++	++	**
CSN	++	++	++	++	++	**
Ekart	NR	–	NR	NR	NR	NR
HD-IMT	NR	NR	NR	NR	NR	NR
Honda	NR	++	NR	++[b]	++[b]	**
IMPROVE	++	++	++	++	++	**
Kato	++	++	++	++	++	**
Landecho	++	++	++	++	++	**
NIGUARDA-MONZINO	++	++	++	++	++	**
OSACA2	+	+	++	++	++	*
Papagianni	++	+	++	++	+	*/**
POPROSTU	++	+	++	++	++	*
RIAS	++	++	++	++	++	**
SPARC	NR	NR	NR	++	++	**
3SCO	++	++	++	++	++	**
Clinical trials						
ACAPS	+	+	+	++	++	**
ALLO-IMT	+	++	+	++	++	*
ASAP-NL	–	–	++	–	–	–
ATIC	+/++	+/++	+/++	–[a]	–[a]	–[a]
AUDITOR	–	–	++	–	–	–
BAS	+	+	+	–	+	–
BK REGISTRY II	++	–	++	++	++	*/**
CAMERA	++	+	++	++	++	**
CAPTIVATE	–	–	++	–	–	–
CERDIA	++	–	++	++	++	**
CONTRAST	+	+	+	++	++	**
EGE STUDY	NR	NR	NR	++	++	**
ENHANCE	–[a]	++	++	++	++	**
FACIT	+	+	+	–	–	*
GRACE	++	++	++	++	++	**
Gresele	++	++	++	++	++	**
HART	++	++	++	++	++	**
KIMVASC	–[a]	–[a]	NR	NR	–	NR

LIFE-ICARUS	++	++	++	++	++	**
Masia	NR	NR	++	NR	–	NR
MAVET	–[a]	–[a]	–[a]	–	–	–
MEDICLAS	–	–	–	+	+	*
MG600	++	++	++	++	++	**
Nakamura II	NR	NR	NR	NR	NR	NR
OPAL	+	+	+	+	+	*
PERIOCARDIO	+	+	+	+	+	**
PREVEND IT	+	–[a]	+	++	++	*
RADIANCE I	+	–	++	++	++	**
RADIANCE II	+	–	++	++	++	**
REGRESS	++	–	++	–[a]	–[a]	–[a]
RIS	++	++	++	++	++	**
Safarova	++	++	++	++	++	*
SECURE	++	++	++	++	++	**
STARR	++	++	++	++	++	**
STOP-NIDDM	++	NR	++	++	++	NR
VITAL	+	+	++	++	++	**
WELCOME	++	++	++	++	++	**

–, not provided; +, self-report only; ++, self-report supplemented by objective criteria (e.g.: electrocardiography, echocardiography, enzymes, imaging); *, based on death certificate only; **, based on death certificate supplemented by medical record; CHD, coronary heart disease; NR, not reported; Full study names and references are provided in **Table S1**. [a]recorded but not provided. [b]fatal events only. [c]cardiovascular disease only.

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